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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,494	05/30/2006	Chieko Kitada	63628 (46342)	8374

21874 7590 08/11/2008

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
08/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,494	KITADA ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *7-11 and 13-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6 and 12* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/14/08, 2/14/08, 6/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-15 and 38-41, and election of the species of metastin derivative, compound 385, and the species of function, treat/prevent hormone-dependent cancers, in the reply filed on 5/15/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The species read on claims 1-6 and12. Claims 7-11 and 13-47 are withdrawn for pertaining to a non-elected invention or species. Compound 385 is free of the prior art. The search was extended to compounds 141, 174, 260, 269, 279, 286, 296, 300, 303, 305, 318, 319, 322, 323 and 386, which were also found to be free of the prior art. Prior art was found on a species in the genus of formula I. Rejections under 35 U.S.C. 112, first paragraph have been made over the species treat/prevent hormone-dependent cancers. Thus, the examination has not been extended beyond these species.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 2/14/2008 and 6/23/2005 includes non-patent literature citations missing the author, title and/or date. These citations were not considered. The IDS must be amended to include the title, date and author of each non-patent literature reference.

Specification

3. The use of the trademark TWEEN-80 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

4. The claims are objected to because the lines are crowded too closely together, making reading difficult. Substitute claims with lines one and one-half or double spaced on good quality paper are required. See 37 CFR 1.52(b).

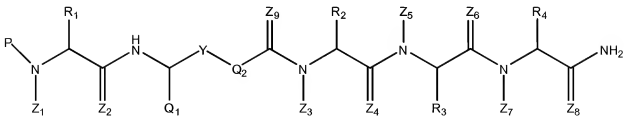
5. Claims 1-6 and 12 are objected to because of the following informalities: the use of parenthetical and bracketed phrases in the claims is confusing, for example, the bracket following formula I in claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6 and 12 are drawn to metastin derivatives of formula (I):



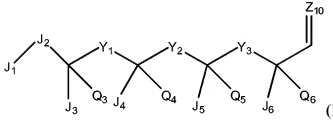
wherein Z_2, Z_4, Z_6, Z_8 and Z_9 are O or S;

Z_1, Z_3, Z_5 and Z_7 are H or C_{1-3} alkyl;

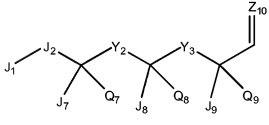
Y is -CONH-, -CSNH-, $-CH_2NH-$, NHCO-, $-CH_2O-$, CH_2S- or $-CH_2CH_2-$, which may be optionally substituted with a C_{1-6} alkyl group;

Q_2 is CH_2, NH or O, which may be optionally substituted;

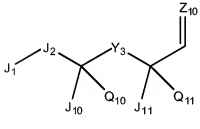
and P is H, an amino acid residue bound from the C-terminal end of the 1-48 sequence of SEQ ID NO: 1, or



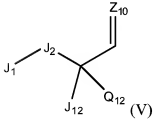
(II) ,



(III),



(IV) or



(V)

wherein Z_{10} is O or S, and

Y_1, Y_2 and Y_3 are -CON(J_{13})-, -CSN(J_{13})-, -C(J_{14})N(J_{13})-, or N(J_{13})CO-, wherein J_{13} and J_{14} are H or C_{1-3} alkyl (additional variables are defined in the claims but are not included here for brevity).

8. The genus encompassed by formula I includes countless species and is not characterized by a common core that can be readily envisaged from this chemical formula. At best, several broad subgenera with characteristic backbone structures can be identified. For example, the embodiments wherein Z_2, Z_4, Z_6, Z_8, Z_9 and Z_{10} are O, Z_1, Z_3, Z_5 and Z_7 are H, Y is -CONH-, Q_2 is CH_2, Y_1, Y_2 and Y_3 are -CON(J_{13})- and J_{13} is H, have a peptide backbone. In these compounds, R_1-R_4 and Q_1-Q_{12} represent side chains. Owing to the broad definition of R_1-R_4 and Q_1-Q_{12} in claim 1, the peptide sequences included in formula I are not limited to the 20 naturally occurring amino acids, but rather encompass a broad range of natural and non-natural amino acids. The derivatives are 6, 10, 9, 8 and 7 amino acid residues in length when P is H, II, III, IV and V, respectively. Given the variable side chains and variable backbone lengths, there are countless species encompassed in the peptide subgenera of formula I. Furthermore, the genus encompasses diverse modifications at the N-terminus (J_1 and J_2). Alternatively, the backbone of the compounds of formula I may not be a peptide. For example, if Z_2, Z_4, Z_6, Z_8, Z_9 and Z_{10} are S, Y is -CSNH-, -CH2NH-, NHCO-, -CH_2O-, CH_2S- or -CH_2CH_2-, Q_2 is NH or O, or Y_1, Y_2 and Y_3 are -CSN(J_{13})-, -C(J_{14})N(J_{13})-, or N(J_{13})CO-, the derivatives have a non-peptide backbone. Any combination of options for each of these variables is permitted creating countless backbones with countless side chains.

9. The USPTO provides claim terms with their broadest reasonable interpretations in light of the specification. As described above, the term "metastin derivative" in claim 1 is structurally

defined in the specification as being represented by formula (I). In addition, the specification limits the genus with functional properties. Paragraph 0375 of the instant specification states that metastin derivatives possess a cancer metastasis suppressing activity or a cancer growth suppressing activity. Claim 5 is limited to agents for suppressing cancer metastasis or proliferation, claim 6 is limited to an agent for treating/preventing cancer and claim 12 is limited to an agent for preventing/treating hormone-dependent cancer.

10. Claims 1, 3-6 and 12 fail to comply with the written description provision of 35 U.S.C. 112, first paragraph, because while the specification recites a chemical formula to define the structure of the genus, it does not correlate the structure to function and in failing to do so, does not describe a genus of compounds that meet both the structural and functional limitations of the claim, in light of the unpredictability and level of skill in the art. That is, while one of skill in the art could conclude that Applicant was in possession of all of the compounds of formula 1 at the time of filing, one could not conclude that Applicant was in possession of the full scope of compounds that meet the structural requirements of formula I and have the functional ability to suppresses cancer metastasis or cancer growth or to treat and/or prevent cancer. The structural and functional limitations must both be described to demonstrate possession of the genus of metastin derivatives. In other words, while it is possible for one of skill in the art to easily recognize whether or not they are in possession of a compound having the structure of formula I, it is not possible for one of skill in the art to easily determine, in light of the specification and the knowledge and skill in the art at the time of filing, whether or not they are in possession of a metastin derivative having the structure of formula I, a metastin derivative being a compound of

formula I having an ability to suppress cancer metastasis or cancer growth. The rejection is further outlined below.

11. In addition claims 1, 3-6 and 12 fail to comply with the enablement provision of 35 U.S.C. 112, first paragraph, because while the specification is enabling for the use of metastin derivatives recited in Tables 1-10 for suppressing cancer metastasis and growth and for treating cancer, it is not enabled for the use of the entire scope of compounds encompassed by formula I or for preventing cancer. Given the state of the prior art at the time of filing, the level of skill in the art, the level of unpredictability in the art, and the lack of guidance in the specification on how to identify active embodiments of formula I, the skilled artisan would not be able to use the full scope of the claim without undue experimentation. The rejection is further outlined below.

12. Claims 1, 3-6 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The factors to be considered are the scope of the claims discussed above and the following:

Actual Reduction to Practice

Compounds 305 and 322, two embodiments of the claimed invention, were actually reduced to practice at the time of filing. The compounds recited in Tables 1-10 were synthesized and assayed for binding properties characteristic of metastin. All of the compounds in Tables 1-10 have peptide backbones and comprise 10 amino acid residues. No compounds having a non-

peptide backbone were synthesized. With respect to the functional property of treating cancer, compounds 305, 232, 206, 303, 322 and 141 were assayed for cell growth inhibition activity in hot7t175-expressed cho cells *in vitro*, and compounds 305 and 322 were evaluated for anti-tumor activity *in vivo* using tumor-bearing mice with human colonic carcinoma-derived cell line SW620.

Disclosure of Drawings or Structural Chemical Formulas

The specification presents formula (I). The specification fails to correlate this structural formula to function and to identify a common core for the genus that is responsible for the claimed function of metastin derivatives.

Relevant Identifying Characteristics of the Genus

Complete structure: The specification presents generic formula I and specifically the compounds in Tables 1-10 as complete structures of metastin derivatives. All of the compounds in Tables 1-10 have peptide backbones, comprise 10 amino acid residues, and are derivatives of the MS10 sequence YNWNSFGLRFNH$_2$ (residues 45-54 of the naturally occurring metastin protein) wherein a substitution or chemical modification is made at 1-5 positions and/or at the N-terminus. No peptide sequences other than these derivatives of MS10 are presented. No compounds having a non-peptide backbone are presented.

Partial Structure: The specification does not present partial structures of metastin derivatives.

Physical and/or chemical properties: The specification does not describe physical and/or chemical properties of metastin derivatives possessing an ability to treat and/or prevent cancer that would allow a skilled artisan to distinguish compounds that meet only the structural

requirements of formula I from compounds that meet both the structural requirements of formula I and the functional requirements of the definition for metastin recited in the specification.

Structure/Function Correlation: The specification does not describe a correlation between the structure of formula I and the functional property of metastin derivatives to suppress cancer metastasis and growth and to treat and/or prevent cancer. Although the specification presents *in vitro* binding data on a large number of compounds, the compounds are not representative of the entire genus. Furthermore, the specification fails to analyze the data to correlate structure and function. Accordingly, the specification fails to provide guidance on the specific structural features of the genus that account for the function of the genus, namely an ability to treat or prevent cancer. Absent this information, the skilled artisan cannot readily envisage specific embodiments of formula I that possess the claimed functional properties. The skilled artisan can not for example read the specification and readily decipher which positions in formula I are critical for function and which can be changed and in what way to preserve function. The lack of this description limits the ability of the skilled artisan to determine whether or not they are in possession of a species of the claimed genus.

Method of Making the Claimed Compounds

Methods of peptide synthesis are routine in the prior art. Methods of determining which peptide sequence to synthesize in order to satisfy both the structural and functional limitations of the claims are not routine.

Level of Skill and Knowledge in the Art

It is not within the skill of those in the art to design peptide with a desired function or to predictably modify the structure of a peptide to alter the function. It is further not within the skill

of those in the art at the time the invention was filed to treat or prevent cancer or to suppress cancer metastasis using metastin or metastin derivatives.

Predictability in the Art

The level of unpredictability in the cancer treatment and prevention art is high. Literature from around the filing date of the instant application describes metastin (also referred to as KISSS1) as having a substantiated physiological role in metastasis suppression but does not identify metastin as a therapeutic target or means. Harms *et al.* ("KISS1 metastasis suppression and emergent pathways," *Clinical and Experimental Metastasis*, **2003**, *20*, 11-18) write:

Metastatic disease is the most critical impediment to cancer patient survival. However, comparatively little is known concerning the intricate pathways which govern the complex phenotypes associated with metastasis. The KISS1 metastasis suppressor gene inhibits metastasis in both *in vivo* melanoma and breast carcinoma models. Despite its clear physiological activity, the mechanism of KISS1 remains unclear. Recent identification of a 54 amino acid peptide of KISS1, termed metastin or kisspeptin-54, and its cognate G-protein coupled receptor (hOT7T175, AXOR12, GPR54) have provided additional clues and avenues of research. While studies have attributed KISS1 with modulation of NFκB regulation, experiments with metastin and its receptor implicate MAP kinase pathways and also suggest the potential of autocrine, paracrine and endocrine roles. Impacts on motility, chemotaxis, adhesion and invasion have each been documented in disparate cell lines and conflicting observations require resolution. Nevertheless, mounting clinical evidence, particularly the loss of KISS1 in metastases, correlates KISS1 and metastin receptor expression with human tumor progression. Together, the data substantiate roles for these molecules in metastasis regulation.

The post-filing date art speculates that metastin is a therapeutic target but has not substantiated this claim. Masui *et al.*, ("Metastin and its variant forms suppress migration of pancreatic cancer cells," *Biochem. Biophys. Res. Com.*, **2004**, *315*, 85-92) write:

Metastin, a post-translationally modified variant of KiSS1, was recently identified as an endogenous peptide agonist for a novel G-protein coupled receptor, hOT7T175 (AXOR12, GPR54). In this study, we analyzed the role of KiSS1 and hOT7T175 in both pancreatic cancer tissues and pancreatic cancer cell lines. Furthermore, we synthesized novel short variant forms of metastin and tested the inhibitory effect of those variants on in vitro cell functions that are relevant to metastasis. Pancreatic cancer tissues showed significantly lower expression of KiSS1 mRNA than normal tissues (p=0.018), while cancer tissues showed significantly higher

expression of hOT7T175 mRNA than normal pancreatic tissues (p=0.027). In human pancreatic cancer cell lines, KiSS1 mRNA was highly expressed in 2 out of 6 pancreatic cancer cell lines, while hOT7T175 mRNA was expressed in all cell lines at various degrees. PANC-1 cells showed the highest expression of hOT7T175. Exogenous metastin did not suppress cell proliferation but significantly reduced the in vitro migration of PANC-1 cells (p<0.01). Metastin induced activation of ERK1 in PANC-1 and AsPC-1 cells. Finally, we synthesized 3 novel short variant forms of metastin, FM053a2TFA, FM059a2TFA, and FM052a4TFA. These metastin variants significantly suppressed the migration of PANC-1 cells and activated ERK1. These data suggest that the metastin receptor, hOT7T175, is one of the promising targets for suppression of metastasis, and that small metastin variants could be an anti-metastatic agent to pancreatic cancer.

In summary, there is a lack of evidence in the prior art that metastin can be used to suppress cancer growth or metastasis and treat/prevent cancer, and there is a merely speculative discussion in the post-filing date art that metastin is a therapeutic target. Therefore, the skilled artisan could not use the knowledge of the art at the time the instant application was filed to determine or not they were in possession of a metastin derivative as claimed, that is whether not a compound having a structure of formula I would also have the functional ability to suppress cancer growth or metastasis or treat/prevent cancer. In the absence of guidance in the prior art, guidance in the specification is required and is, as discussed above, insufficient to determine possession.

When the above factors are weighed, one of ordinary skill in the art would not recognize that Applicant was in possession of the claimed genus of metastin derivatives at the time of filing. The compounds presented in Tables 1-10, which are all derivatives of the MS10 peptide, are not representative of the entire genus of formula I which includes peptides of different lengths and non-peptide compounds. Furthermore, the compounds presented in Tables 1-10 are not representative of the entire sub-genus of peptide compounds of formula I in light of the breadth of the sub-genus, the lack of structure/function correlation presented in the specification

and the level of skill and unpredictability in the peptide design and cancer treatment and prevention art. Only the compounds recited in Tables 1-10 meet the written description requirement of 35 U.S.C. 112, first paragraph.

13. Claims 1, 3-6 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using metastin derivatives recited in Tables 1-10 of the specification, does not reasonably provide enablement for making and using the entire scope of the genus encompassed by formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The factors considered as set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) are addressed as follows:

The Nature of the Invention and the breadth of the claims

The claims are drawn to metastin derivatives of formula I. The breadth of the claims were outlined above.

The State of the Prior Art

Literature from around the filing date of the instant application describes metastin (also referred to as KISSS1) as having a substantiated physiological role in metastasis suppression but does not identify metastin as a therapeutic target or means. Harms *et al.* ("KISS1 metastasis suppression and emergent pathways," *Clinical and Experimental Metastasis*, **2003**, *20*, 11-18) write:

Metastatic disease is the most critical impediment to cancer patient survival. However, comparatively little is known concerning the intricate pathways which govern the complex phenotypes associated with metastasis. The KISS1 metastasis suppressor gene inhibits metastasis

in both *in vivo* melanoma and breast carcinoma models. Despite its clear physiological activity, the mechanism of KISS1 remains unclear. Recent identification of a 54 amino acid peptide of KISS1, termed metastin or kisspeptin-54, and its cognate G-protein coupled receptor (hOT7T175, AXOR12, GPR54) have provided additional clues and avenues of research. While studies have attributed KISS1 with modulation of NFκB regulation, experiments with metastin and its receptor implicate MAP kinase pathways and also suggest the potential of autocrine, paracrine and endocrine roles. Impacts on motility, chemotaxis, adhesion and invasion have each been documented in disparate cell lines and conflicting observations require resolution. Nevertheless, mounting clinical evidence, particularly the loss of KISS1 in metastases, correlates KISS1 and metastin receptor expression with human tumor progression. Together, the data substantiate roles for these molecules in metastasis regulation.

The prior art does not report the structures of metastin derivatives that can be used to suppress cancer metastasis or growth or treat/prevent cancer.

The Predictability or Unpredictability of the Art

The post-filing date art speculates that metastin is a therapeutic target but has not substantiated this claim. Masui *et al.*, ("Metastin and its variant forms suppress migration of pancreatic cancer cells," *Biochem. Biophys. Res. Com.*, **2004**, *315*, 85-92) write:

Metastin, a post-translationally modified variant of KiSS1, was recently identified as an endogenous peptide agonist for a novel G-protein coupled receptor, hOT7T175 (AXOR12, GPR54). In this study, we analyzed the role of KiSS1 and hOT7T175 in both pancreatic cancer tissues and pancreatic cancer cell lines. Furthermore, we synthesized novel short variant forms of metastin and tested the inhibitory effect of those variants on in vitro cell functions that are relevant to metastasis. Pancreatic cancer tissues showed significantly lower expression of KiSS1 mRNA than normal tissues (p=0.018), while cancer tissues showed significantly higher expression of hOT7T175 mRNA than normal pancreatic tissues (p=0.027). In human pancreatic cancer cell lines, KiSS1 mRNA was highly expressed in 2 out of 6 pancreatic cancer cell lines, while hOT7T175 mRNA was expressed in all cell lines at various degrees. PANC-1 cells showed the highest expression of hOT7T175. Exogenous metastin did not suppress cell proliferation but significantly reduced the in vitro migration of PANC-1 cells (p<0.01). Metastin induced activation of ERK1 in PANC-1 and AsPC-1 cells. Finally, we synthesized 3 novel short variant forms of metastin, FM053a2TFA, FM059a2TFA, and FM052a4TFA. These metastin variants significantly suppressed the migration of PANC-1 cells and activated ERK1. These data suggest that the metastin receptor, hOT7T175, is one of the promising targets for suppression of metastasis, and that small metastin variants could be an anti-metastatic agent to pancreatic cancer.

Jiang *et al.* ("*KiSS1* Suppresses Metastasis in Human Ovarian Cancer via Inhibition of Protein Kinase C Alpha," *Clinical and Experimental Metastasis*, **2005**, *22*, 369-376) write:

Metastasis is a vital target for cancer treatment, since the majority of cancer patients die from metastatic, rather than the primary disease. *KiSS1* has been identified as a metastasis suppressor gene in melanoma and breast carcinomas. We show here that *KiSS1* is also a metastasis suppressor in human ovarian cancer. Overexpression of *KiSS1* in ovarian cancer cells inhibits cell migration induced by serum or lysophosphatidic acid (LPA), and colonization in soft agar, but not cell proliferation, representing the characteristics of a metastasis suppressor gene. Furthermore, using an experimental metastatic mouse model, we show that expression of *KiSS1* in SKOV3 ovarian cancer cells suppresses >50% metastatic colonization in mice ($P < 0.0001$). We find that activating protein kinase C (PKC) reverses about 80% of the inhibited cell migration induced by *KiSS1*, while down-regulation of PKCα with shRNA restores *KiSS1* effect, providing evidence that inhibiting PKCα may be an important mechanism of the effect of *KiSS1*. These results suggest that *KiSS1* is a metastasis suppressor of ovarian cancer and may be a potential molecular target for the treatment.

Nash *et al.* ("The KISS1 metastasis suppressor: mechanistic insights and clinical utility," *Front. Biosci.*, **2006**, *11*, 647-59) write:

We were the first to show that the introduction of *KISS1* into highly metastatic human melanoma cell lines C8161 and MelJuSo suppressed metastases to the lung by >95% following intravenous or orthotopic injection (8,9,33). Interestingly, introduction of *KISS1* into a metastatic breast cancer cell line MDA-MB-435 also showed a >95% suppression of metastases to the lung following orthotopic injection (33). Those data strongly suggested *KISS1* metastasis suppression may be pertinent in tumors of widely different origins, a conclusion borne out in subsequent studies (11,30,37–40), albeit of varying quality and significance. In general, loss or reduction of *KISS1* expression in several different tumor types inversely correlates with tumor progression, metastatic potential and survival. The data summarized below highlights the potential value of KISS1 as an important clinical target for the prognostication and treatment of metastatic disease.

Despite many of the unresolved questions, KISS1 remains a promising molecular target for the treatment of metastatic disease and has shown great promise as a prognostic indicator for several cancers. However, greater efforts need to be made in the characterization of KISS1 metastasis suppression before its clinical value can be determined.

In summary, there is a lack of evidence in the prior art that metastin can be used to suppress cancer growth or metastasis and treat/prevent cancer, and there is a merely speculative

discussion in the post-filing date art that metastin is a therapeutic target. Therefore, the skilled artisan could not use the knowledge of the art at the time the instant application was filed to predict whether or not a compound having a structure of formula I would also have the functional ability to suppress cancer growth or metastasis or treat/prevent cancer. In the absence of guidance in the prior art, guidance in the specification is required and is, as discussed below, insufficient to determine allow for predictable use of the claimed compounds.

The Relative Skill of Those in the Art

Methods of peptide synthesis are routine in the prior art. Methods of determining which peptide sequence to synthesize in order to satisfy both the structural and functional limitations of the claims are not routine. It is not within the skill of those in the art to design peptide with a desired function or to predictably modify the structure of a peptide to alter the function. It is further not within the skill of those in the art at the time the invention was filed to treat or prevent cancer or to suppress cancer metastasis using metastin or metastin derivatives.

The Amount of Direction or Guidance Presented

The specification presents generic formula I and specifically the compounds in Tables 1-10 as examples of metastin derivatives. All of the compounds in Tables 1-10 have peptide backbones, comprise 10 amino acid residues, and are derivatives of the MS10 sequence YNWNSFGLRFNH_2 (residues 45-54 of the naturally occurring metastin protein) wherein a substitution or chemical modification is made at 1-5 positions and/or at the N-terminus. No peptide sequences other than the compounds of Tables 1-10 which share 5-9 common residues with MS10. No compounds having a non-peptide backbone are presented. The specification does not describe physical and/or chemical properties of metastin derivatives possessing an

ability to treat and/or prevent hormone-dependent cancer that would allow a skilled artisan to predict if compounds that meet the structural requirements of formula I also meet the functional requirements of the definition for metastin recited in the specification. The specification does not describe a correlation between the structure of formula I and the functional property of metastin derivatives to suppress cancer metastasis and growth and to treat and/or prevent cancer. Although the specification presents *in vitro* binding data on a large number of compounds, the specification fails to analyze the data in terms of a structure/activity relationship. Accordingly, the specification fails to provide guidance on the specific structural features of the genus that account for the function of the genus, namely an ability to treat cancer. Absent this information, the skilled artisan cannot readily predict if specific embodiments of formula I will also exhibit the claimed functional properties of the genus. The skilled artisan can not for example read the specification and readily decipher which positions in formula I are critical for function and which can be changed and in what way to preserve function. The lack of this guidance limits the ability of the skilled artisan to predict whether or not a compound can be used.

The Presence or Absence of Working Examples

Compounds 305 and 322, two embodiments of the claimed invention, were actually reduced to practice at the time of filing. The compounds recited in Tables 1-10 were synthesized and assayed for binding properties characteristic of metastin. All of the compounds in Tables 1-10 have peptide backbones and comprise 10 amino acid residues. No compounds having a non-peptide backbone were synthesized. With respect to the functional property of treating cancer, compounds 305, 232, 206, 303, 322 and 141 were assayed for cell growth inhibition activity in hot7t175-expressed cho cells *in vitro*, and compounds 305 and 322 were evaluated for anti-tumor

activity *in vivo* using tumor-bearing mice with human colonic carcinoma-derived cell line SW620. The specification is enabled for the use of compounds 305 and 322 because the specification clearly established with experimental *in vivo* data that the compounds are functional. It would be routine for the skilled artisan to select additional species from Tables 1-10 and test in animal models described in the specification for an ability to suppresses cancer metastasis or growth.

In contrast, the working examples provided in the specification are not sufficient to enable the use of the entire scope of formula I. The compounds recited in Tables 1-10 of the specification are closely related to the metastin peptide that has been studied in the prior art and correlated to a physiological role in metastasis and speculated to be a therapeutic target. The scope of the claims is significantly broader that the scope exemplified by these species. There is nothing in the prior art or the specification to suggest that compounds other than those recited in the tables can be used to as metastin derivatives.

Furthermore, because the metastin-related metastasis is only one mechanism by which cancer metastasizes, inhibition of this mechanism can not prevent cancer growth resulting from all other mechanisms. Therefore, the working examples presented in the specification are insufficient to enable all compounds, including 305 and 322, for use in cancer prevention.

The Quantity of Experimentation Necessary

Considering the factors above, the skilled artisan would be burdened with undue experimentation in determining if one of the claimed compounds would be effective at suppressing cancer metastasis or growth and treating/preventing cancer. The skilled artisan would be burdened with testing a broad range of compounds of formula I in *in vitro* binding

assays. The active compounds would then have to be subjected to animal models of cancer growth and metastasis. The experimentation required represents years of inventive effort. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Therefore, in view of the *Wands* factors, the claims appear to require undue experimentation to use the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 3-6 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Stafford *et al.* (*Cancer Research.*, **2002**, *62*, 5399-5404, reference CB on Information Disclosure Statement filed 4/14/2008). Stafford *et al.* teach the peptide YNWNSFGLRY (KiSS1 peptide, Figure 1). With respect to formula I, P is YNWN (amino acids 45-48 of SEQ ID NO: 1). The amino acid sequence YNWN is consistent with the formula J^1-J^2-$C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})$- wherein: J^1, J^3, J^4, J^5 and J^6 are H; J^2 is NH; Q^3 is the side chain of tyrosine, a C_1 alkyl group substituted with a C_6 aromatic hydrocarbon group substituted with hydroxyl; Q^4 is the side chain of asparagine, a C_1 alkyl group substituted with an amide group; Q^5 is the side chain of tryptophan, a C_1 alkyl group substituted with a 9-membered aromatic fused heterocyclic group consisting of 8 carbons and 1 nitrogen; Q^4 is the side chain of asparagine, a C_1 alkyl group substituted with an amide group; Y^1, Y^2 and Y^3

represent -CON(J^{13})- wherein J^{13} is H; and Z^{10} is O. With respect to the remainder of formula I, Z^1, Z^3, Z^7 are H; Z^2, Z^4, Z^6 and Z^8 are O; R^1 is the side chain of serine, a C_1 alkyl group substituted with hydroxyl; R^2 is the side chain of leucine, a C_4 alkyl group; R^3 is the side chain of arginine, a C_3 alkyl group substituted with a basic group; and R^4 is the side chain of tyrosine, a C_1 alkyl group substituted with a C_6 aromatic hydrocarbon group substituted with hydroxyl. Finally, with respect to variable X, Q^1 is the side chain of phenylalanine, a C_1 alkyl group substituted with a C_6 aromatic hydrocarbon group; Y is -CONH-; Q^2 is CH_2; and Z^9 is O. The peptide sequence is not found in SEQ ID NO: 1. Thus, the peptide meets all the structural limitations of claims 1, 3-15 and 38-41.

With respect to claim 3, Stafford *et al.* teach mKiSS1 and hKiSS1, each of which comprise the peptide YNWNSFGLRY. These longer proteins may undergo proteolytic cleavage to yield the 10 amino acid peptide YNWNSFGLRY. Therefore, mKiSS1 and hKiSS1 are prodrugs of the peptide YNWNSFGLRF which is a species of formula I.

With respect to claim 4, Stafford *et al.* teach a composition comprising KiSS1 peptide and FBS and LiCl (Materials and Methods page 5401, PLC-β Assay).

With respect to claims 5, 6 and 12, neither Kotani *et al.* or Stafford *et al.* teach that the kisspeptin-10 or KiSS1 peptide can suppress cancer metastasis, suppress cancer proliferation, treat or prevent cancer, or treat or prevent hormone-dependent cancer. Because the chemical structure of the species taught by Kotani *et al.* and Stafford *et al.* are identical to species within the claimed genus, the prior art species inherently meet these additional functional limitations. The discovery and characterization of properties of a known material do not make it novel (see MPEP § 2112). Furthermore, there is no requirement that a person of ordinary skill in the art

would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference (see MPEP § 2112). If the composition is physically the same, it must have the same functional properties. A chemical composition and its properties are inseparable. Because the prior art of Kotani *et al.* and Stafford *et al.* teach the identical chemical structure as the claimed genus, the functional properties applicant claims are necessarily present (see MPEP § 2112.01). Examiner cannot however determine whether or not kisspeptin-10 or KiSS1 peptide taught by Kotani *et al.* and Stafford *et al.*, respectively, inherently possesses properties which anticipate or render obvious the claimed invention but has basis for shifting the burden of proof to applicant. See MPEP § 2112.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1, 3-6 and 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6 of copending application

11/977,477. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 3-6 and 12 are generic to all that is recited in claim 6 of copending application 11/977,477. That is claim 6 of copending application 11/977,477 falls entirely within the scope of claims 1, 3-6 and 12 or, in other words, claims 1, 3-6 and 12 are anticipated by claim 6 of copending application 11/977,477. Specifically, claim 6 of copending application recites:

Ac-D-Tyr-Hyp-Asn-Thr-Cha-Gly-Ala(cPr)-Arg(Me)-Trp-NH2,

Ac-D-Tyr-Hyp-Asn-Thr-Cha-GlyΨ((E)CH=CH)-Leu-Arg(Me)-Trp-NH2,

Ac-D-Tyr-Hyp-Alb-Thr-Cha-GlyΨ((E)CH=CH)-Leu-Arg(Me)-Trp-NH2,

Ac-D-Tyr-Hyp-Asn-Thr-Cha-GlyΨ((E)CH=CH)-Leu-Arg-Trp-NH2,

Ac-D-Tyr-Hyp-Alb-Thr-Cha-GlyΨ((E)CH=CH)-Leu-Arg-Trp-NH2,

Ac-D-Tyr-Hyp-Alb-Thr-Cha-Gly-Ala(cPr)-Arg(Me)-Trp-NH2 and

Ac-D-Tyr-Pro(4F)-Asn-Thr-Cha-Gly-Ala(cPr)-Arg(Me)-Trp-NH2,

with respect to formula I, Z_2, Z_4, Z_6, Z_8, Z_9 and Z_{10} are O, Z_1, Z_3, Z_5 and Z_7 are H, Y is -CONH-, Q_2 is CH_2, Y_2 and Y_3 are -CON(J_{13})-, J_7, J_8, J_9, and J_{13} are H, and Q_7, Q_8, Q_9, R_1, Q_1, Q_2, R_2, R_3 and R_4 correspond to the side chains of amino acids 1-9, respectively.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 1, 3-6 and 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 50 of copending application 11/630,698. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 3-6 and 12 are generic to all that is recited in claim 50 of

copending application 11/630,698. That is claim 50 of copending application 11/630,698 falls entirely within the scope of claims 1, 3-6 and 12 or, in other words, claims 1, 3-6 and 12 are anticipated by claim 50 of copending application 11/630,698. Specifically, claim 6 of copending application recites compound 305 and 385 which are identical to those in the instant specification. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

19. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654